Markovnikov Alcohols via Epoxide Hydroboration
by Molecular Rock-Forming Metal Catalysts

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Abstract: Synthesis of branched “Markovnikov” alcohols is crucial to various chemical industries. The catalytic reduction of substituted epoxides under mild conditions is a highly attractive method for preparing such alcohols. Classical methods based on heterogeneous or homogeneous transition metal-catalyzed hydrogenation, hydroboration or hydroxylation usually suffer from poor selectivity, reverse regioselectivity, limited functional group compatibility, high cost and/or low availability of the catalysts. Here we report the discovery of a highly regioselective (up to 99%) hydroboration of nonsymmetrical epoxides catalyzed by-ligated alkali metal triethylborohydride, an old archetypal reductant in organic chemistry. The chemoselectivity and turnover efficiencies of the present catalytic approach are excellent. Thus, terminal and internal epoxides with ene, yne, aryl, and halo groups were selectively and quantitatively reduced under a substrate-to-catalyst ratio (S/C) of up to 1000.

One Sentence Summary: Both terminal and internal epoxides are hydroborated-hydrolyzed to give secondary alcohols using ligated MHBEt3 (M = alkali metal, Et = ethyl) under mild conditions and with high regioselectivity and turnover efficiencies, and tolerance to C=C, C≡C and halo functional groups.

Main Text: Markovnikov alcohols are important chemicals with myriad applications in bulk/fine agrochemicals, pharmaceuticals, and fragrance industries. Thus, their synthesis is continuously of great interest. Petroleum-derived olefins are currently the largest-volume building blocks to access alcohols. Mono- or polysubstituted olefins can give two regioisomeric alcohols in the general case (1-3). Markovnikov alcohols, in which the hydroxyl group is bound to the more substituted one of two adjacent carbons (Fig. 1), can be obtained from such olefins by liquid or solid acid catalysed hydration or a two-step Wacker oxidation-reduction process. However, due to the frequent limitations of these transformations (isomerization, cyclization, poor catalyst performance, equilibria issues and/or force conditions employed, limited functional group tolerance, chemoselectivity), stoichiometric oxymercuration-demercuration (4), catalytic Mukaiyama hydration (5) as well as enzymatic hydration (6) reactions emerged as more efficient methods (Fig. 1).
The reduction of strained triangular epoxides, easily obtainable from olefins via epoxidation, is an alternative method of preparing alcohols (1). The combination of appropriately regioselective and functional-group-tolerant reduction with the inexpensive and selective epoxidation of olefins will permit the two-step synthesis of functionalized alcohols. Conventional methods for the epoxide ring-opening are based on stoichiometric amounts of strong reducing agents such as LiAlH₄. Such methods usually suffer from poor regioselectivities by providing a mixture of both primary and secondary alcohols, poor functional group tolerance and the generation of enormous amounts of waste. Heterogeneous (7-9) and particularly homogeneous transition-metal catalysed hydrogenation (1, 10), hydroboration (11-13), and hydrosilylation (14-20) of epoxides as well as transition-metal-free approaches (11, 14, 21) were developed by several laboratories leading preferentially to anti-Markovnikov alcohols. Many fewer catalysts have been reported for the selective reduction of epoxides into Markovnikov alcohols. Examples include heterogeneous (22) and homogeneous hydrogenation (23-25) as well as transfer hydrogenation (26) with precious metals (Ru, Rh, Pd), substrate limited hydrosilylation with Zn (27), and high-catalyst loading hydroboration with alkaline-earth Mg (28). Noyori-type molecular catalysts based on precious Ru (23, 24) are particularly regio- and/or chemoselective methods, but are either limited to terminal epoxides (23, 24) or monosubstituted epoxides (24), and/or are not tolerant to terminal C=C bonds (23). Selective reduction of unsymmetrical epoxides bearing terminal and internal double bonds leading to olefinic Markovnikov alcohols would be of particular value (29).

Here we report an example of highly selective epoxide ring-opening protocol catalysed by major rock-forming non-transition metal-based species being some of the most abundant metals.
in the Earth’s crust (M = Li, Na and K). We found that readily available and inexpensive off-the-shelf alkali metal triethylborohydrides in the presence of a ligand catalyze highly regio- and chemoselective hydroboration of substituted epoxides producing secondary alcohols in excellent yields and with broad functional group tolerance.

Inspired by the recently discovered catalytic activity of traditional reducing agent LiAlH₄ (30), we attempted to reduce model substrate styrene oxide 8a by pinacolborane (HBpin) with a catalytic amount of LiAlH₄ as well as more common NaBH₄ and KBH₄ reagents under neat conditions (Scheme S1). In all cases negligible (~20) turnovers were detected. Furthermore, similarly poor activity was found for corresponding saline MH (M = Li, Na, K) hydrides (Scheme S1). Delightfully, we found that stronger reducing agents such as MHBE₃ (M = Li, Na, K; Et = ethyl) are one-order more efficient for the same reaction, leading to a promising total of ~500 turnovers (Scheme S1). Moreover, consistent with the stoichiometric reduction of epoxides with these reagents, the regioselectivity of ~9:1 was noted in favor of Markovnikov product. Inspired by this notable activity and promising selectivity, we further tested the same reactions in the presence of 1 equiv. of various commercially available mono- and polydentate organic ligands (Scheme S2). Based on 102 tested reactions, a ligand was found to generally have a beneficial effect on both the catalytic efficiency and regioselectivity. For example, the reaction yield increased to ~ 99% from an average of 40%, whereas the regioselectivity reached up to a ~40:1 ratio in the best cases.

In the next step, by using two promising ligands for both efficiency and selectivity, namely 2,2’:6’,2″-terpyridine (tpy or L17) and 18-crown-6 (L31), we attempted to isolate active catalytic species and reaction intermediates. For M/L17 (M = Li, Na and K) and M/L31 (M = Na and K), isolable complexes 1–5 were obtained in moderate-to-appreciable yields and characterized by NMR spectroscopies and X-ray crystallography (Fig. 2 and SI). The reaction of styrene oxide with isolated 2 and 5 afforded products 6 and 7, respectively, the regioselectivity of which is consistent with the Markovnikov formulation.
Fig. 2. Isolation of active catalytic species and possible reaction intermediates in the hydroboration of styrene oxide catalyzed by MHBEt₃ (M = Na, K; Et = ethyl) in the presence of 1 equiv. of L₁₇ and L₃₁ ligands. X-ray structures are drawn with ellipsoids at 30% probability level. Non-critical H-atoms are omitted. The X-ray structure of 3 is isostructural to 2, see SI.

Notably, all the isolable complexes 1–7 are active catalyst precursors for the hydroboration of styrene oxide (Scheme S3). Furthermore, complexes 1–7 feature even improved activity and/or selectivity relevant to the in situ 1:1 M[HB₃Et₃]/ligand reactivity (Scheme S2 and S3). We particularly noted 30:1 Markovnikov selectivity achieved with complexes 2 or 3 in the quantitative
 (>99%) hydroboration of styrene oxide under neat conditions (Scheme S3). Next, we compared the efficiency of 1–7 with various homogeneous catalysts from our laboratories, popular commercially available metal–ligand bifunctional catalysts, classical precious metal catalyst precursors, as well as MgBu₂ being the state-of-the-art catalyst for Markovnikov epoxide hydroboration (28) (Scheme S3). Under identical conditions employed, all the complexes based on transition metals screened were found to be very poor catalysts. Furthermore, all complexes 1–7 provide significantly higher activity and selectivity for this reaction relative to MgBu₂, placing them in the category of most-efficient catalysts reported to date for the reaction under study.

In the next step, after proper optimization of the reaction conditions as summarized in Table S2, we tested the scope for the hydroboration of various simple and functional epoxides 8 catalyzed by 2 under solvent-free conditions (Fig. 3).

**Fig. 3.** Conditions: epoxides (1.0 mmol), pinacolborane (1.1 mmol) and 2 (0.1 mol%, S/C = 1000), neat, rt, N₂, 2 h (to ensure completion of reactions). Complete conversion unless otherwise described. Isolated yields and ratios of two
regioisomers determined by GC analysis using hexamethylbenzene as an internal standard. *Reaction run in THF (1 mL) for 16 h, 75% conversion. †NMR yield with hexamethylbenzene as an internal standard. ‡Reaction run in THF (1 mL) at 80 ºC for 16 h, 55% conversion.

Delightfully, we found that epoxides 8 were quantitatively reduced in the presence of such reducible groups as terminal and internal ene, yne, aryl and halo by using only 0.1 mol% catalyst loading, and the corresponding secondary alcohols 9 were isolated in good to high yields after hydrolysis. We also noted that the regioselectivity remains on very high level (25:1 to 99:1) for all substrates tested except 4-fluorostyrene oxide that affords Markovnikov alcohol with 12:1 regioselectivity. The potential application of our catalyst in industrial synthesis of Markovnikov alcohols was demonstrated on the example of 8f hydroboration performed at 10 mmol scale (see Scheme S4). Thus 1.34 g of the corresponding product 9f was isolated in 88% yield from the reaction where only 5.4 mg of catalyst 2 was used (S/C = 1000).

Next, we performed a deuterium-labeling experiment, kinetics studies and computational analysis based on density functional theory (DFT) aimed at building the mechanistic understanding of 2-catalyzed hydroboration. Here, our goal was to decipher the role that the sodium cation, the anion and the tpy ligand alone and altogether played in the catalytic reaction. A further goal was to identify the regioselectivity-determining step and probe the identity of the catalytic cycle. Full details are available in the SI, and here we would like to summarize the most important findings.

Hydroboration of styrene oxide with DBpin shows >50:1 Markovnikov selectivity with deuterium atom incorporation at the less-substituted methylene group. The regioselectivity thus nearly doubled relative to HBpin, where a 30:1 ratio was observed. The corresponding product PhCH(OH)CH₂D was isolated in 90% yield (Scheme S5). The initial rates method indicates that the catalytic reaction displays first-order dependence on both styrene oxide and HBpin concentrations and one-half order in 2 concentration leading to approximately the following rate equation in tetrahydrofuran: \( \frac{d[\text{product}]}{dt} \sim k[\text{styrene oxide}]^1[\text{HBpin}]^1[2]^{0.5} \) with \( k \approx 0.39 \text{ min}^{-1} \text{ M}^{-1.5} \) at 25 ºC, see SI. Kinetic studies thus indicate that both styrene oxide and HBpin enter the rate-determining zone of the catalytic cycle as well as corroborate the mononuclear reactivity of 2, which therefore dissociates into two fragments under catalytic conditions.

To uncover the role that the sodium cation, the [HBEt₃]⁻ anion and the tpy ligand play in the regioselectivity-determining step, we have chosen the substrate 8f that affords the product 9f with the appreciably high regioselectivity of >99% in the computational analysis. Various transition states were sampled based on plausible bimolecular and trimolecular combinations (see SI). The optimized geometries of the most energetically accessible transition states are shown in Fig. 4A.
Fig. 4. A. Geometries of optimized transition states determining Markovnikov vs anti-Markovnikov selectivities in the hydroboration of 8f based on [HBEt₃]⁻, [HBEt₃]Na⁺ and [HBEt₃]Na⁺(tpy) species. B. Catalytic cycle for 8a hydroboration catalysed by 2, suggested by combined computational analysis and kinetics data. Non-critical H-atoms and all non-covalent interactions with Na are omitted for clarity for the optimized transition state structures. All relative standard free energies are reported in kcal⋅mol⁻¹.

For naked [HBEt₃]⁻, computations predict the highest regioselectivities based on a computed 5.5 kcal⋅mol⁻¹ energy gap between transition states TSₐ–TSₖ. Addition of sodium to the model leads to the change of the molecularity and decrease of the energy gap to 2.6 kcal⋅mol⁻¹ between transition states leading to Markovnikov and anti-Markovnikov products, transition states TSₕ–TSₖ. Thus, the role of the ligand is likely to decrease the Lewis acidity of the cation via its coordination which leads to the increase of regioselectivity towards Markovnikov product. Computational analysis manifested in the transition states TSₙ–TSₖ does reproduce the observed regioselectivity for [HBEt₃]⁻Na(tpy)⁺, but does not capture ligation effect, as the energy gap between two transition states is expected to lie between 2.6 and 5.5 kcal⋅mol⁻¹. The computed energy gap of 1.5 kcal⋅mol⁻¹ between determining transition states TSₙ–TSₖ rather suggests for either poor sampling achieved and/or is the virtual result of computational accuracy of the single-reference DFT method being at least ~3 kcal⋅mol⁻¹, see SI. Furthermore, separate experiments indicated that catalytic reactions with [HBEt₃]⁻Na⁺ in the presence of 1 or 2 equiv of tpy all showed comparable regioselectivity with varying yields (Scheme S2). This suggests that full isolation of the cation via coordination of two ligands does not happen under catalytic conditions. This statement is also in agreement with the catalytic properties of 1 being a six-coordinate metal-complex precatalyst, which does not show regioselectivity increase relative to other precatalysts (Scheme S3). The involvement of the monoligated cation in the catalytic process is further manifested from the unveiled catalytic cycle for styrene oxide 8a hydroboration with 2 based on combined computational analysis and kinetic data, see SI and Fig. 4B. Here species int₀ and int₁ serve as active intermediates whereas rate-determining transition state TSᵢ represents concerted epoxide ring-opening by [HBEt₃]⁻ anion and HBpin.
In summary, we report a convenient catalytic protocol for the synthesis of Markovnikov alcohols via hydroboration of epoxides in the presence of old and cheap “stoichiometric” reagents MHBET$_3$ (M = Li, Na, K) which become efficient catalysts in the presence of various chelating ligands such as terpyridine, crown ethers or others. Isolable complexes such as 1–7 can be also used for this reaction often providing even better catalytic activity and reaction regioselectivity. The method is tolerant to various functional groups, which further adds value to the present catalytic system. Computational analysis and kinetic studies indicate that both the [HBE$_3$]$^-$ anion and alkali metal cation are equally important for the catalytic activity. The former determines catalytic efficiency, whereas the latter controls the reaction selectivity. The crucial factor for achieving high regioselectivity is decreased Lewis acidity of the alkali metal cation. This is achieved by the ligation of the alkali metal cation by the appropriate ligand containing electron-rich heteroatoms. Analysis of the catalytic cycle indicates that both rate- and regioselectivity-determining transition state of this reaction is concerted HBpin-assisted epoxide ring-opening by the [HBE$_3$]$^-$ anion. The ligated alkali metal cation plays an important role within the catalytic cycle to establish a three-dimensional molecular assembly stabilized by non-covalent interactions.

References and Notes:


29. The opposite chemoselectivity, namely, the hydroboration of alkyne epoxides leading to saturated epoxides, has precedents, see for example: A. D. Ibrahim, S. W. Entsminger, A. R. Fout, Insights into a Chemoselective Cobalt Catalyst for the Hydroboration of Alkenes and Nitriles. ACS Catal. **7**, 3730-3734 (2017).


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